Docket No. CDS-59

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Thomas Arter, et al.

Serial No. : 08/493,442 Art Unit: 1211

Filed : June 22, 1995 Examiner: R. Gitomer

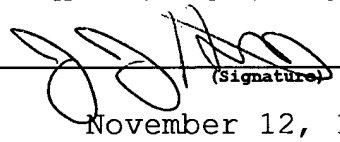
For : DRY ANALYTICAL ELEMENT FOR ACETAMINOPHEN ASSAY

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on

November 12, 1997

James J. Harrington

Name of applicant, assignee, or Registered Representative



(Signature)

November 12, 1997

(Date of Signature)

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

BRIEF ON APPEAL

This is an appeal from a Final Rejection dated May 27, 1997, a Notice of Appeal having been filed on August 27, 1997.

STATUS OF ALL CLAIMS:

Claims 1-8 and 12 have been cancelled.

Claims 9-11 and 13-17 have been finally rejected under 35 U.S.C. 103 and are all presented for appeal.

STATUS OF AMENDMENTS FILED SUBSEQUENT TO FINAL REJECTION:

Applicants amendment filed on August 25, 1997 was considered by the U.S. Patent Office was not entered and is therefore not of Official record for purposes of this appeal.

CONCISE SUMMARY OF THE INVENTION:

The present invention, as claimed, is directed to a dry analytical element, and a method which incorporates the analyical element, for determining acetominophen in an aqueous fluid. The analytical element comprises: a) a water soluble color-forming coupling agent, b) a fericyanide oxidating agent capable of oxidatively coupling para-aminophenol to the water soluble color forming coupling agent, c) at least one layer comprising gelatin, and, d) a buffer capable of providing a pH in the range between about pH 6.5 to 8.5.

The art teaches chemical problems which at the time of this invention would have been expected to prevent the success of the instant analytical element. These problems include gelatin hardening at the alkaline pH thought to be required for oxidative dye formation, and the undesirability of using ferricyanide as an oxidizing agent.

CONCISE STATEMENT OF ALL ISSUES PRESENTED FOR REVIEW:

I. Whether claims 9-11, 14 and 17 are obvious under 35 U.S.C. 103(a) over the combination of the Arter reference (Clinical Chemistry July 1993) or the Hammond Reference ("Development of an Enzyme Based Assay for Acetomenophen") in view of either U.S. Patent 4, 675,290 (Matsumoto) or U.S. Patent 4, 999,288 (Decastro) and in further view of U.S. Patent 4,845,030 (Batz).

II. Whether claims 13, 15 and 16 are obvious under 35 U.S.C. 103 (a) as being unpatentable over the combination of the Arter reference (clinical Chemistry, July 1993) or the Hammond reference ("Development of an Enzyme Based Assay for Acetomenophen") in view of either U.S. Patent 4, 675,190 (Matsumoto) or U.S. Patent 4,999,288 (Decastro) and further in view of U.S. Patent 4,820,649 (Kawaguchi).

GROUPING OF CLAIMS:

For the purpose of this Appeal, the following groups of claims do not stand of fall together:

Group I., including claims 9-11 and 14, is directed to a dry multilayer analytical element for the determination of acetomenophen in an aqueous fluid,comprising a support.

Group II., including claim 17 is directed to a method for determination of acetamenophen in an aqueous liquid.

ARGUMENT BY APPELLANT WITH RESPECT TO EACH OF THE ISSUES PRESENTED

I. The Rejections:

A. Claims 9-11, 14 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Arter or Hammond in view of either Matsumoto or decastro and in further view of Batz.

B. Claims 13, 15, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Arter or Hammond in view of either Matsumoto or deCastro and in further view of Batz as applied to claims 9-11, 14, 17 and further in view of U.S. patent 4,820,649 (Kawaguchi).

The Patent Office states it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the oxidising enzyme and coupling agents disclosed in the Matsumoto and deCastro references in the determination of Arter and Hammond because the reactions employed for the determinations are nearly identical and Matsumoto and deCastro provide motivation for employing coupling agents and oxidising enzymes. The Patent Office states that to employ coupling agents to enhance color formation is well known in the art. The Patent Office states that both Matsumoto and deCastro employ oxidising agents and enzymes for the same function as claimed in the present invention.

The Patent Office further states that the Batz patent teaches structure I which encompasses the presently claimed coupling agent, 1-(3-sulfopropyl)-1,2,3,4-tetrahydroquinoline. The Patent Office concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the specific coupling agent of Batz in the determinations of Arter, Hammond, Matsumoto and deCastro because Matsumoto and deCastro teach closely related coupling agents for the same function as presently claimed.

The Patent Office further states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the maleimide of Kawaguchi in the test strips of the above references because maleimide would have its expected fuction, reducing interferences.

B. Current U.S. Law Relating to Obviousness:

The consistent criteria for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that the invention should be carried out and would have a reasonable liklihood of success, viewed in the light of the prior art. Both the suggestion and expectation of success must be

founded in the prior art, not in applicants disclosure. *In re Dow Chemical Co. 5 USPQ 2d 1529 (Fed. Cir. 1988).*

The interface between prohibited hindsight, permissible combined reference obviousness and improper "obvious to try" concepts was delineated in *Uniroyal Inc. v. Rudkin-Wiley Corp., USPQ 2d 1434 (Fed. Cir. 1988).*

Clearly, the "obvious to try" standard is inadequate to render the claimed invention obvious without some teaching in the prior art which gives a reasonable expectation of success in achieving that goal. *In re O'Farrell, 7 USPQ 2d 1673 (Fed. Cir. 1988).*

C. Discussion:

Claims 9-11, 14 and 17 are not obvious over the combination of Arter or Hammond in view of either Matsumoto or deCastro and in further view of Batz.

Claims 13, 15, and 16 are not obvious over the combination of Arter or Hammond in view of either Matsumoto or deCastro and in further view of Batz as applied to claims 9-11, 14, 17 and further in view of U.S. patent 4,820,649 (Kawaguchi).

The present invention, as claimed, is directed to a dry analytical element, and a method which incorporates the analytical element, for determining acetominophen in an aqueous fluid. The analytical element comprises: a) a water soluble color-forming coupling agent, b) a fericyanide oxidating agent capable of oxidatively coupling para-aminophenol to the water soluble color forming coupling agent, c) at least one layer comprising gelatin, and d) a buffer capable of providing a pH in the range between about pH 6.5 to 8.5.

DISCUSSION OF CITED REFERENCES INDIVIDUALLY:

Individually, none of the references cited disclose or even suggest the presently claimed dry analytical element or the method which incorporates the element.

The **Arter** reference deals generall with an assay for acetomenophen. However, Arter does not disclose or even suggest the use of ferricyanide. The Arter reference teaches the use of ascorbate acid oxidase (AAO) to couple p-amino phenol to the THQ.

Hammond teaches an aqueous method of determining acetaminophen using an arylacylamidase to catalyze hydrolysis of acetaminophen. The catalysis produces p-aminophenol, which is then converted to a dye via oxidation. The reference teaches that this conversion occurs with sufficient sensitivity and rapidity *only at a pH of greater than 9.2* (Fig. 1, page 155). This teaching is also mentioned in the subject specification (page 1, lines 34-36). However, as is stated in the specification, gelatin hardening is accelerated at such alkaline pH. The problems of anticipated gelatin hardening and the anticipated slow oxidation of p-aminophenol at a more acidic pH were *unexpectedly overcome* in the claimed dry analytical element using ferricyanide salts (page 3, lines 11-26). Therefore, the presently claimed invention is entirely different from and would not be obvious over the disclosure in Hammond.

Matsumoto teaches a method for condensing aromatic amines with certain aromatic couplers to form dye in solution. Matsumoto fails to teach or suggest the necessity of water-soluble couplers, a claimed element of the present invention.

Moreover, the reference even fails to teach or suggest the couplers of the instant claims. The species of couplers which Matsumoto does teach do not even have the properties required in the instant invention (see Table II, pp 15 and 16 of the specification, couplers 6, 7, 8, and 9). Therefore, the presently claimd invention is entirely different from and would not be obvious over the disclosure in Matsumoto.

deCastro teaches a method of stabilizing arylacylamidase using phenol derivatives. These derivatives may also serve as coupling agents to produce chromogens upon oxidative condensation with p-aminophenol. deCastro does not disclose or suggest dry analytical elements comprising gelatin. In fact, deCastro *teaches away* from using ferricyanide salts as oxidizing agents, as is done in the claimed invention. Specifically, deCastro teaches that such oxidative coupling is catalyzed by Fe III under alkaline conditions (col 2, lines 1-16). deCastro teaches further that *Fe III is not desirable* and that a "novel catalyst/oxidant" is required, such as periodates (col 2, lines 62 -68, bridging col 3, lines 1-8). Therefore there would be no motivation to change the known methods and use Fe III under neutral pH conditions. Clearly, the scope and content of the prior art at the time of the present invention taught that research should be directed in other areas. The applicants proceeded "contrary to accepted wisdom" in the art. That the present inventors achieved the claimed invention by doing what those skilled in the art suggested should not be done is a fact strongly probative on nonobviousness. *Kloster Speedsteel AB v. Crucible Inc. 230 USPQ 81 (Fed. Cir. 1986).*

Batz teaches the use of aniline derivatives as coupling agents for determining oxidizing agents such as hydrogen peroxide or Fe III. Batz teaches the use of 1-(3-sulfopropyl)-1,2,3,4-

tetrahydroquinoline. However, Batz fails to teach or suggest dry analytical elements, the use of the disclosed couplers in dry formulations, or the combination of ferricyanide salts with these couplers.

Kawaguchi teaches the use of maleimide to couple proteins and antibodies to polymeric materials to suspend them in their element. The patent does not teach or suggest the present assay directed to a dry analytical element for determining acetominophen in an aqueous fluid which uses a fericyanide oxidating agent at pH 6.5 to 8.5. The present assay does not even use maleimide for reducing interferences.

COMBINING THE TEACHINGS OF THE CITED REFERECES

There must be some logical reason or motivation, apparent from positive concrete evidence of record, which justifies a combination of primary and secondary references, *In re Regel 526 F.2d 1399 (CCPA 1975)*. Applicants submit that the Patent Office has shown no motivation to combine the teachings of the cited references. The present application's specification teaches that the couplers of Matsumoto do not yield the desired performance in dry analytical elements. Batz does not teach or suggest dry analytical elements or the requirement for water-soluble couplers therein. None of these references even suggests dry analytical elements -- let alone dry analytical elements comprising gelatin and, therefore, the unexpected utility of ferricyanide salts.

Additionally, one of ordinary skill in the art would not seek to modify the assays and methods of Hammond to employ ferricyanide salts as oxidizing agents in view of deCastro, because deCastro teaches that such oxidizing agents are undesirable. In addition, the express statements made in deCastro teaches away from the basis for combining the

references. An express statement in one of the references whose combination is relied upon, teaching away from the alleged basis for combination may defeat obviousness grounded in combining the reference teachings. *In re Grasselli, 218 USPQ 769, 780 (Fed. Cir. 1983).*

A careful reading of the prior art references show that no motivation to combine the references is found and that the Patent Office has used impermissible hindsight reconstruction, using applicants specification as a guide to support the obviousness rejection.

Even if motivation was found to combine the teachings of the cited references the many differences between the broadest claim of the present case and the cited prior art make it clear that no combination would result in the invention of the rejected claim. Obviousness cannot be determined using the applicants disclosure as a template or blueprint and selecting elements from the prior art to fill in the gaps. *In re Gormon, 18 USPQ 2d 1885 (Fed. Cir. 1991).*

Modification of the assay compositions and methods described by Hammond or Arter with the teachings of Matsumoto in light of Batz does not lead to the instant invention. Even if the teachings of Hammond, deCastro, and Batz were combined, one would not expect to obtain the instant invention as claimed. Although deCastro mentions elements comprising filter paper, there is no teaching or suggestion that these elements comprise gelatin. Accordingly, no combination of the cited references teaches or suggests all of the elements of the instant invention.

SURPRISING RESULTS:

Unexpected advantages or surprising results are strong evidence on non-obviousness. *In re Margolis 228 USPQ 940 (Fed. Cir. 1986)*

In addition, an invention that solves a long-felt need in the industry leads to an inference of non-obviousness. *Dow Chemical Co. v. American Cyanamid Co., 2 USPQ2d 1350 (Fed. Cir. 1987).*

The presently claimed analytical element *surprisingly* overcomes problems known in the art in at least two important ways. First, the ferricyanide oxidizing agent, as used in this invention, would have been *expected to fail* as a suitably rapid oxidizing agent within the neutral pH range used here. This expectation of failure is based on the relative weakness of Fe^{+++} as an oxidizing agent compared to other metal oxidizing agents (*see, e.g.*, Table A, page 19 of the specification). Unexpectedly, however, the ferricyanide used in this element permits the very rapid generation of a detectable colored signal -- in only *57 seconds* (*see* page 4, line 29 of the specification).

Second, the ferricyanide, as used in this invention, would have been expected to *chemically attack* the gelatin matrix also present in the element. This attack would have resulted in gelatin hardening due to chemical crosslinking, which in turn would have prevented the element from functioning properly (*see, e.g.*, page 3, lines 14-16 of the specification). Surprisingly, however, the ferricyanide does not behave this way in the claimed analytical element. Rather, one skilled in the art would appreciate that this analytical element possesses a *non-hardening* gelatin component as one of its *unexpected* features.

Applicants maintain that *each* of these two unexpected advantages would, *by itself*, render the claimed analytical element non-obvious over the cited combinations of references. *At best*, these combinations merely describe certain components of the claimed analytical element. Their combined teachings fail to

provide an expectation of success, or even an impetus to try, regarding the instant invention.

CONCLUSION:

Claims 9-11, 14 and 17 are not obvious over the combination of Arter or Hammond in view of either Matsumoto or deCastro and in further view of Batz.

Claims 13, 15, and 16 are not obvious over the combination of Arter or Hammond in view of either Matsumoto or deCastro and in further view of Batz as applied to claims 9-11, 14, 17 and further in view of U.S. patent 4,820,649 (Kawaguchi)

Respectfully Submitted,

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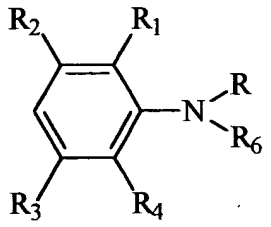
CLAIMS AS CURRENTLY ON APPEAL:

9. A dry multilayer analytical element for the determination of acetaminophen in an aqueous fluid, comprising a support having thereon, in order from said support and in fluid contact:

(a) a layer having therein (i) an arylacylamidase enzyme; (ii) a ferricyanide capable of oxidatively coupling paraaminophenol to a color-forming coupling agent to form a color compound; and (iii) a water-soluble, color-forming coupling agent , at least one layer comprising gelatin and said water-soluble, color-forming coupling agent having the general formula:



wherein R is a water-solubilizing group selected from (1) $-(CH_2)_nX$, where n is 1 to 5, X is either (I) $-SO_3M$ where M is hydrogen, an alkali metal, an alkaline earth metal or an ammonium (NH_4^+) cation, or (II) $(-OCH_2CH_2)_yOH$ where y is 2 to 5; and (2) $-N(R_7)_3^+Z-$ where each R_7 is independently selected from alkyl of 1 to 4 carbon atoms, and Z is an acid anion;

R_1 and R_6 are taken together to represent an ethylene, trimethylene, or tetramethylene group which forms a partially saturated ring; and

R_2, R_3, and R_4 are independently selected from hydrogen, alkyl of 1 to 4 carbon atoms, and alkoxy of 1 to 4 carbon atoms;

(b) a porous spreading layer; and

(c) a buffer which maintains the pH of the element in a range of between about 6.5 to 8.5.

10. The element of claim 9 wherein the ferricyanide is a ferricyanide salt of an alkali metal.

11. The element of claim 9 wherein the coupling agent is 1-(3-sulfopropyl)-1,2,3,4-tetrahydroquinoline.

13. The element of claim 9 further containing maleimide.

14. The dry multilayer analytical element of claim 9 for the determination of acetaminophen in an aqueous fluid comprising a support having thereon, in order from said support

(a) a first and second reagent layer wherein the first reagent layer contains therein 1-(3-sulfopropyl)-1,2,3,4-tetrahydroquinoline, and the second reagent layer contains therein a ferricyanide salt and arylacylamidase; and

(b) a porous spreading layer.

15. The element of claim 14 further containing maleimide.

16. The element of claim 15 wherein the maleimide is in the spreading layer.

17. A method for determining acetaminophen in an aqueous liquid comprising the steps of:

(a) contacting a sample of aqueous liquid with the analytical element of claim;

(b) determining the amount of color compound formed; and

(c) correlating the amount of color compound formed to the concentration of acetaminophen in the fluid.